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(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of provisional application Ser. No. 60/066,804, filed November 26, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bd306_7 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone bd306_7 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:2;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265; the nucleotide sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265; the nucleotide sequence of the full-length protein coding sequence of clone bd306_7 deposited under accession number ATCC 98599; or the

nucleotide sequence of a mature protein coding sequence of clone bd306_7 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 148 to amino acid 189. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:2, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 195 to amino acid 204 of SEQ ID NO:2.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:1, but excluding the poly(A) tail at the 3' end of SEQ ID NO:1; and

(ab) the nucleotide sequence of the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:1, but excluding the poly(A) tail at the 3' end of SEQ ID NO:1; and

(bb) the nucleotide sequence of the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:1 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:1 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:1. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 148 to amino acid 189;

(c) fragments of the amino acid sequence of SEQ ID NO:2 comprising eight consecutive amino acids of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 148 to amino acid 189. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:2, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 195 to amino acid 204 of SEQ ID NO:2.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 719 to nucleotide 1855;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 779 to nucleotide 1855;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fj283_11 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fj283_11 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone fj283_11 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone fj283_11 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:4;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 719 to nucleotide 1855; the nucleotide sequence of SEQ ID NO:3 from nucleotide 779 to nucleotide 1855; the nucleotide sequence of the full-length protein coding sequence of clone fj283_11 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone fj283_11 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone fj283_11 deposited under accession number ATCC 98599. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 27. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:4.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:3, but excluding the poly(A) tail at the 3' end of SEQ ID NO:3; and

(ab) the nucleotide sequence of the cDNA insert of clone fj283_11 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:3, but excluding the poly(A) tail at the 3' end of SEQ ID NO:3; and

(bb) the nucleotide sequence of the cDNA insert of clone fj283_11 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:3, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:3 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:3 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:3. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:3 from nucleotide 719 to nucleotide 1855, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:3 from nucleotide 719 to nucleotide 1855, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:3 from nucleotide 719 to nucleotide 1855. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:3 from nucleotide 779 to nucleotide 1855, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:3 from nucleotide 779 to nucleotide 1855, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:3 from nucleotide 779 to nucleotide 1855.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 27;

(c) fragments of the amino acid sequence of SEQ ID NO:4 comprising eight consecutive amino acids of SEQ ID NO:4;

(d) the amino acid sequence encoded by the cDNA insert of clone fj283_11 deposited under accession number ATCC 98599; and

(e) the amino acid sequence encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 27. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:4.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 982 to nucleotide 2118;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 1042 to nucleotide 2118;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 621 to nucleotide 1248;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fj283_6 deposited under accession number ATCC xxxxx;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx;

(g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone fj283_6 deposited under accession number ATCC xxxxx;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:4;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:32 from nucleotide 982 to nucleotide 2118; the nucleotide sequence of SEQ ID NO:32 from nucleotide 1042 to nucleotide 2118; the nucleotide sequence of SEQ ID NO:32 from nucleotide 621 to nucleotide 1248; the nucleotide sequence of the full-length protein coding sequence of clone fj283_6 deposited under accession number ATCC xxxxx; or the nucleotide sequence of a mature protein coding sequence of clone fj283_6 deposited under accession number ATCC xxxxx. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 184 to amino acid 193 of SEQ ID NO:4.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:32.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32; and

(ab) the nucleotide sequence of the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32; and

(bb) the nucleotide sequence of the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:32 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:32 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:32. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32 from nucleotide 982 to nucleotide 2118, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:32 from nucleotide 982 to nucleotide 2118, to a nucleotide

sequence corresponding to the 3' end of said sequence of SEQ ID NO:32 from nucleotide 982 to nucleotide 2118. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32 from nucleotide 1042 to nucleotide 2118, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:32 from nucleotide 1042 to nucleotide 2118, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:32 from nucleotide 1042 to nucleotide 2118. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32 from nucleotide 621 to nucleotide 1248, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:32 from nucleotide 621 to nucleotide 1248, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:32 from nucleotide 621 to nucleotide 1248.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fk317_3 deposited under accession number ATCC 98599;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599;

(e) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone fk317_3 deposited under accession number ATCC 98599;

(f) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:6;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624; the nucleotide sequence of the full-length protein coding sequence of clone fk317_3 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone fk317_3 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 72. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:6, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 56 to amino acid 65 of SEQ ID NO:6.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:5, but excluding the poly(A) tail at the 3' end of SEQ ID NO:5; and

(ab) the nucleotide sequence of the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:5, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:5; and

(bb) the nucleotide sequence of the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:5 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:5 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:5. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 72;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising eight consecutive amino acids of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 72. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:6, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 56 to amino acid 65 of SEQ ID NO:6.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone k213_2x deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone k213_2x deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:8;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578; the nucleotide sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578; the nucleotide sequence of the full-length protein coding sequence of clone k213_2x deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone k213_2x deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:8, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 32 to amino acid 41 of SEQ ID NO:8.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:7, but excluding the poly(A) tail at the 3' end of SEQ ID NO:7; and

(ab) the nucleotide sequence of the cDNA insert of clone k213_2x deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:7, but excluding the poly(A) tail at the 3' end of SEQ ID NO:7; and

(bb) the nucleotide sequence of the cDNA insert of clone k213_2x deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:7 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:7 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:7. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8 comprising eight consecutive amino acids of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:8, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 32 to amino acid 41 of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone na316_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone na316_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:10;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598; the nucleotide sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598; the nucleotide sequence of the full-length protein coding sequence of clone na316_1 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone na316_1 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:10, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 39 to amino acid 48 of SEQ ID NO:10.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:9, but excluding the poly(A) tail at the 3' end of SEQ ID NO:9; and

(ab) the nucleotide sequence of the cDNA insert of clone na316_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:9, but excluding the poly(A) tail at the 3' end of SEQ ID NO:9; and

(bb) the nucleotide sequence of the cDNA insert of clone na316_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:9 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:9 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:9. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10 comprising eight consecutive amino acids of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:10, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 39 to amino acid 48 of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone nf93_20 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone nf93_20 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:12;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986; the nucleotide sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986; the nucleotide sequence of the full-length protein coding sequence of clone nf93_20 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone nf93_20 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:12, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 100 to amino acid 109 of SEQ ID NO:12.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:11, but excluding the poly(A) tail at the 3' end of SEQ ID NO:11; and

(ab) the nucleotide sequence of the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:11, but excluding the poly(A) tail at the 3' end of SEQ ID NO:11; and

(bb) the nucleotide sequence of the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:11 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:11 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:11. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:11 from

nucleotide 408 to nucleotide 986, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) fragments of the amino acid sequence of SEQ ID NO:12 comprising eight consecutive amino acids of SEQ ID NO:12; and

(c) the amino acid sequence encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:12, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 100 to amino acid 109 of SEQ ID NO:12.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone np164_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone np164_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:14;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821; the nucleotide sequence of the full-length protein coding sequence of clone np164_1 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone np164_1 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:14, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 248 to amino acid 257 of SEQ ID NO:14.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:13, but excluding the poly(A) tail at the 3' end of SEQ ID NO:13; and

(ab) the nucleotide sequence of the cDNA insert of clone np164_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:13, but excluding the poly(A) tail at the 3' end of SEQ ID NO:13; and

(bb) the nucleotide sequence of the cDNA insert of clone np164_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:13 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:13 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:13. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID

NO:13 from nucleotide 1381 to nucleotide 1821, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) fragments of the amino acid sequence of SEQ ID NO:14 comprising eight consecutive amino acids of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:14, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 248 to amino acid 257 of SEQ ID NO:14.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pe204_1 deposited under accession number ATCC 98599;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599;

(e) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone pe204_1 deposited under accession number ATCC 98599;

(f) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:16;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537; the nucleotide sequence of the full-length protein coding sequence of clone pe204_1 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone pe204_1 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:16, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:16.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:15, but excluding the poly(A) tail at the 3' end of SEQ ID NO:15; and

(ab) the nucleotide sequence of the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:15, but excluding the poly(A) tail at the 3' end of SEQ ID NO:15; and

(bb) the nucleotide sequence of the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:15, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:15 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:15 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:15. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) fragments of the amino acid sequence of SEQ ID NO:16 comprising eight consecutive amino acids of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:16, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ya1_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ya1_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:18;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109; the nucleotide sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109; the nucleotide sequence of the full-length protein coding sequence of clone ya1_1 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone ya1_1 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:18, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 176 to amino acid 185 of SEQ ID NO:18.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:17, but excluding the poly(A) tail at the 3' end of SEQ ID NO:17; and

(ab) the nucleotide sequence of the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:17, but excluding the poly(A) tail at the 3' end of SEQ ID NO:17; and

(bb) the nucleotide sequence of the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:17 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:17 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:17. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:17 from

nucleotide 1050 to nucleotide 1109, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) fragments of the amino acid sequence of SEQ ID NO:18 comprising eight consecutive amino acids of SEQ ID NO:18; and

(c) the amino acid sequence encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:18, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 176 to amino acid 185 of SEQ ID NO:18.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone yb8_1 deposited under accession number ATCC 98599;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599;

(g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone yb8_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:20;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734; the nucleotide sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734; the nucleotide sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604; the nucleotide sequence of the full-length protein coding sequence of clone yb8_1 deposited under accession number ATCC 98599; or the nucleotide sequence of a mature protein coding sequence of clone yb8_1 deposited under accession number ATCC 98599. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20 from amino acid 70 to amino acid 236. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:20, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 113 to amino acid 122 of SEQ ID NO:20.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:19, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:19; and

(ab) the nucleotide sequence of the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:19, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:19; and

(bb) the nucleotide sequence of the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:19 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:19 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:19. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide

734, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 70 to amino acid 236;

(c) fragments of the amino acid sequence of SEQ ID NO:20 comprising eight consecutive amino acids of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 70 to amino acid 236. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:20, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 113 to amino acid 122 of SEQ ID NO:20.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature forms) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have

determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "bd306_7"

A polynucleotide of the present invention has been identified as clone "bd306_7". bd306_7 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bd306_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bd306_7 protein").

The nucleotide sequence of bd306_7 as presently determined is reported in SEQ ID NO:1, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bd306_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 11 to 23 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the bd306_7 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bd306_7 should be approximately 3700 bp.

The nucleotide sequence disclosed herein for bd306_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bd306_7 demonstrated at least some similarity with sequences identified as AA027096 (zk04d03.s1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 469541 3'), AA027135 (zk04d03.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 469541 5'), AA166312 (ms42g11.r1 Life Tech mouse embryo 13 5dpc 10666014 Mus musculus cDNA clone 614276 5' similar to TR E238793 E238793 DUALIN), AA535890

(nf94a03.s1 NCI_CGAP_Co3 Homo sapiens cDNA clone IMAGE:927532), H14467 (yl25g07.r1 Homo sapiens cDNA clone 159324 5' similar to contains HGR repetitive element), T21281 (Human gene signature HUMGS02637), T61016 (Total DNA sequence from cosmid clones LP(2)127 and LP(2)128), U47621 (Human nucleolar autoantigen No55 mRNA, complete cds), W51808 (zc48g04.r1 Soares senescent fibroblasts NbHSF Homo sapiens cDNA clone 325590 5' similar to PIR:S20742 S20742 synaptonemal complex protein Sc65 - rat; contains Alu repetitive element; mRNA sequence), and X97607 (G.gallus mRNA for cartilage associated protein). The predicted amino acid sequence disclosed herein for bd306_7 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted bd306_7 protein demonstrated at least some similarity to sequences identified as R95913 (Neural thread protein [Homo sapiens]), U47621 (nucleolar autoantigen No55 [Homo sapiens]), and X97607 (cartilage associated protein [Gallus gallus]). Two regions of bd306_7 protein (amino acids 148-217 and 298-367 of SEQ ID NO:2) align with the same region, amino acids 145-214, of cartilage associated protein. The homology between bd306_7 protein and nucleolar autoantigen No55 is also good, but in this case it appears that bd306_7 amino acids 148-189 is similar to two regions of No55 (amino acids 145-186 and 296-337), and bd306_7 amino acids 298-367 are also similar to nearly the same two regions of No55 (amino acids 145-214 and 296-365). This implies that two regions in bd306_7 (roughly 148-189 and 298-367) are similar to each other, and one copy of this region is found in cartilage associated protein, but both are present in No55. Cartilage associated protein is reported to be localized to the extracelluar matrix {J. Cell Sci 1997 110(Pt 12):1351-1359}, while No55 is found in the granular component of the nucleolus {Mol Biol Cell 1996 7(7):1015-1024}. Based upon sequence similarity, bd306_7 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of bd306_7 also indicates that it may contain an Alu repetitive element.

Clone "fj283_11" and Clone "fj283_6"

Polynucleotides of the present invention have been identified as clone "fj283_11" and clone "fj283_6". fj283_11 and fj283_6 were isolated from a human adult lung carcinoma cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or were identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of

the encoded protein. fj283_11 and fj283_6 are full-length clones, including the entire coding sequence of a secreted protein (also referred to herein as "fj283 protein").

The nucleotide sequence of fj283_11 as presently determined is reported in SEQ ID NO:3, and includes a poly(A) tail. The nucleotide sequence of fj283_6 as presently determined is reported in SEQ ID NO:32, and includes a poly(A) tail. Although cDNA clones fj283_11 and fj283_6 have different nucleotide sequences, perhaps as a result of alternative splicing of a common primary mRNA transcript (particularly between nucleotide 402 and nucleotide 618 of SEQ ID NO:32), these clones are predicted to encode the same protein. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the fj283 protein corresponding to the foregoing nucleotide sequences is reported in SEQ ID NO:4. Amino acids 8 to 20 of SEQ ID NO:4 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 21. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the fj283 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone fj283_11 should be approximately 3350 bp. The EcoRI/NotI restriction fragment obtainable from the deposit containing clone fj283_6 should be approximately 2700 bp.

The nucleotide sequences disclosed herein for fj283_11 and fj283_6 were searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. fj283_11 and/or fj283_6 demonstrated at least some similarity with sequences identified as AA052962 (zl70c02.s1 Stratagene colon (#937204) Homo sapiens cDNA clone 509954 3' similar to gb D14531 60S RIBOSOMAL PROTEIN L9 (HUMAN)), AA080949 (zn04d12.r1 Stratagene hNT), AA160948 (zq40e12.r1 Stratagene hNT neuron (#937233) Homo sapiens cDNA clone 632206 5'), AA195089 (zr34c02.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 665282 5', mRNA sequence), AA258887 (zs32b02.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:686859 5'), H97993 (yw06e03.s1 Homo sapiens cDNA clone 251452 3'), R19768 (yg40g06.r1 Homo sapiens cDNA clone 34951 5'), U09953 (Human ribosomal protein L9 mRNA, complete cds), Z73639 (Human DNA sequence from cosmid V389H8 on chromosome X; Contains mRNA near btk gene involved in a-gamma-globulinemia, ESTs, STS), and Z73901 (Human DNA sequence from cosmid V389H8, between markers DXS366 and DXS87 on chromosome X contains pseudogene, mRNA near btk gene involved in a-gamma-globulinemia, ESTs, STSs). The predicted amino acid sequence

disclosed herein for the fj283 protein was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted fj283 protein demonstrated at least some similarity to sequences identified as AB011084 (KIAA0512 protein [Homo sapiens]) and U09953 (ribosomal protein L9 [Homo sapiens]). Based upon sequence similarity, fj283 proteins and each similar protein or peptide may share at least some activity. Profile hidden markov model analysis has revealed the presence of an Armadillo/beta-catenin-like domain within the predicted fj283 protein sequence. The armadillo multigene family comprises many proteins widely differing in sizes and functions which have in common a variable number of tandemly repeated arm sequences of about 42 amino acids in length. Many, but not all, armadillo-repeat-containing proteins are nuclear in localization. The predicted fj283 protein does not appear to be of the nuclear variety, but rather appears to be an extracellular protein.

Clone "fk317_3"

A polynucleotide of the present invention has been identified as clone "fk317_3". fk317_3 was isolated from a human adult kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. fk317_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "fk317_3 protein").

The nucleotide sequence of fk317_3 as presently determined is reported in SEQ ID NO:5, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the fk317_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone fk317_3 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for fk317_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. fk317_3 demonstrated at least some similarity with sequences identified as AA568588 (nm21b11.s1 NCI_CGAP_Co10 Homo sapiens cDNA clone IMAGE:1060797), AC002326 (Genomic sequence from Human 6, complete sequence), H48562 (yq78g07.s1 Homo sapiens cDNA clone 201948 3' similar to contains Alu repetitive element; contains MER30 repetitive element), T67164 (Human alpha-N-

acetylglucosaminidase gene), and Z46941 (H.sapiens DNA for alu repeats). The predicted amino acid sequence disclosed herein for fk317_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted fk317_3 protein demonstrated at least some similarity to sequences identified as X55777 (put. ORF [Homo sapiens]). Based upon sequence similarity, fk317_3 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the fk317_3 protein sequence centered around amino acid 42 of SEQ ID NO:6. The nucleotide sequence of fk317_3 indicates that it may contain an Alu repetitive element.

Clone "k213_2x"

A polynucleotide of the present invention has been identified as clone "k213_2x". Secreted cDNA clones were first isolated from a murine adult bone marrow (stromal cell line FCM-4) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or were identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. These murine cDNAs were then used to isolate k213_2x, a full-length human cDNA clone, including the entire coding sequence of a secreted protein (also referred to herein as "k213_2x protein").

The nucleotide sequence of k213_2x as presently determined is reported in SEQ ID NO:7, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the k213_2x protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8. Amino acids 26 to 38 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 39. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the k213_2x protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone k213_2x should be approximately 1900 bp.

The nucleotide sequence disclosed herein for k213_2x was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. k213_2x demonstrated at least some similarity with sequences identified as AA123852 (mp96e08.r1 Soares 2NbMT Mus musculus cDNA clone 577094 5'), AA362005 (EST71348 T-cell lymphoma Homo sapiens cDNA 5' end), AA436477

(zv08f05.s1 Soares NhHMPu S1 Homo sapiens cDNA clone 753057 3'), AA436528 (zv08f05.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 753057 5'), AA643506 (nq86f04.s1 NCI_CGAP_Co9 Homo sapiens cDNA clone IMAGE:1159231, mRNA sequence), F13485 (H. sapiens partial cDNA sequence; clone c-3dh08), and T19502 (Human gene signature HUMGS00560). Based upon sequence similarity, k213_2x proteins and each similar protein or peptide may share at least some activity.

Clone "na316_1"

A polynucleotide of the present invention has been identified as clone "na316_1". na316_1 was isolated from a human adult brain (corpus callosum) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. na316_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "na316_1 protein").

The nucleotide sequence of na316_1 as presently determined is reported in SEQ ID NO:9, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the na316_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10. Amino acids 30 to 42 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 43. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the na316_1 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone na316_1 should be approximately 900 bp.

The nucleotide sequence disclosed herein for na316_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database. The TopPredII computer program predicts two potential transmembrane domains within the na316_1 protein sequence, centered around amino acids 31 and 66 of SEQ ID NO:10, respectively.

Clone "nf93_20"

A polynucleotide of the present invention has been identified as clone "nf93_20". nf93_20 was isolated from a human adult brain (substantia nigra) cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. nf93_20 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "nf93_20 protein").

The nucleotide sequence of nf93_20 as presently determined is reported in SEQ ID NO:11, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the nf93_20 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 6 to 18 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 19. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the nf93_20 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone nf93_20 should be approximately 2000 bp.

The nucleotide sequence disclosed herein for nf93_20 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. nf93_20 demonstrated at least some similarity with sequences identified as AA063620 (ze87g07.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 366012 3'), AA317410 (EST19337 Retina II Homo sapiens cDNA 5' end), H29417 (ym60e07.r1 Homo sapiens cDNA clone 52631 5'), and N41425 (yw93e08.r1 Homo sapiens cDNA clone 259814 5'). Based upon sequence similarity, nf93_20 proteins and each similar protein or peptide may share at least some activity.

Clone "np164_1"

A polynucleotide of the present invention has been identified as clone "np164_1". np164_1 was isolated from a human fetal kidney (293 cell line) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. np164_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "np164_1 protein").

The nucleotide sequence of np164_1 as presently determined is reported in SEQ ID NO:13, and includes a poly(A) tail. What applicants presently believe to be the proper

reading frame and the predicted amino acid sequence of the np164_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Amino acids 348 to 360 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 361. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the np164_1 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone np164_1 should be approximately 2100 bp.

The nucleotide sequence disclosed herein for np164_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. np164_1 demonstrated at least some similarity with sequences identified as N63143 (yz37c12.s1 Homo sapiens cDNA clone 285238 3'), T19992 (Human gene signature HUMGS01129), Z46676 (Caenorhabditis elegans cosmid C08B11, complete sequence), and Z74910 (S.cerevisiae chromosome XV reading frame ORF YOR002w). The predicted amino acid sequence disclosed herein for np164_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted np164_1 protein demonstrated at least some similarity to sequences identified as Z46676 (C08B11.8 [Caenorhabditis elegans]) and Z74910 (ORF YOR002w [Saccharomyces cerevisiae]). Based upon sequence similarity, np164_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts ten potential transmembrane domains within the np164_1 protein sequence, centered around amino acids 4, 114, 165, 229, 293, 322, 360, 386, 436, and 465 of SEQ ID NO:14, respectively.

Clone "pe204_1"

A polynucleotide of the present invention has been identified as clone "pe204_1". pe204_1 was isolated from a human adult blood (chronic myelogenous leukemia K5) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. pe204_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "pe204_1 protein").

The nucleotide sequence of pe204_1 as presently determined is reported in SEQ ID NO:15, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the pe204_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 116 to 128 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 129. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the pe204_1 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone pe204_1 should be approximately 1100 bp.

The nucleotide sequence disclosed herein for pe204_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. pe204_1 demonstrated at least some similarity with sequences identified as AA279961 (zs92h08.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone 704991 3'), AA306911 (EST178043 Colon carcinoma (HCC) cell line Homo sapiens cDNA 5' end), AC002086 (Human PAC clone DJ525N14), AC002094 (Genomic sequence from Human 17, complete sequence), T97749 (ye58c04.s1 Homo sapiens cDNA clone), Z74696 (Human DNA sequence from cosmid 203C2, between markers DXS6791 and DXS8038 on chromosome X contains ESTs), Z80901 (Human DNA sequence from cosmid N119A7 on chromosome 22q12-qter), and Z82245 (Human DNA sequence *** SEQUENCING IN PROGRESS *** from clone 799F10; HTGS phase 1). The predicted amino acid sequence disclosed herein for pe204_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted pe204_1 protein demonstrated at least some similarity to sequences identified as K02113 (Gallus gallus vitellogenin [Gallus gallus]). Based upon sequence similarity, pe204_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts two additional potential transmembrane domains within the pe204_1 protein sequence, one centered around amino acid 50 and another around amino acid 90 of SEQ ID NO:16.

Clone "ya1_1"

A polynucleotide of the present invention has been identified as clone "ya1_1". ya1_1 was isolated from a human adult testes cDNA library and was identified as

encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ya1_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ya1_1 protein").

The nucleotide sequence of ya1_1 as presently determined is reported in SEQ ID NO:17, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ya1_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 330 to 342 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 343. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the ya1_1 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ya1_1 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for ya1_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ya1_1 demonstrated at least some similarity with sequences identified as AA431507 (zw76e05.r1 Soares testis NHT Homo sapiens cDNA clone 782144 5') and F03332 (H. sapiens partial cDNA sequence; clone c-1tg07). Based upon sequence similarity, ya1_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts two potential transmembrane domains within the ya1_1 protein sequence centered around amino acid 156 and around amino acid 332 of SEQ ID NO:18, respectively. The nucleotide sequence of ya1_1 indicates that it may contain an Alu repetitive element.

Clone "yb8_1"

A polynucleotide of the present invention has been identified as clone "yb8_1". yb8_1 was isolated from a human fetal brain cDNA library and was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. yb8_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "yb8_1 protein").

The nucleotide sequence of yb8_1 as presently determined is reported in SEQ ID NO:19, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the yb8_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 69 to 81

are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 82. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the yb8_1 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone yb8_1 should be approximately 1800 bp.

The nucleotide sequence disclosed herein for yb8_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. yb8_1 demonstrated at least some similarity with sequences identified as AA418057 (zv97a06.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 767698 5' similar to TR:G1143719 G1143719 RS-REX-B), L10334 (Homo sapiens neuroendocrine-specific protein B (NSP) mRNA, complete cds), U17603 (Rattus norvegicus rS-Rex-s mRNA, complete cds), and W19986 (zb38e09.r1 Soares parathyroid tumor NbHPA Homo sapiens cDNA clone 305896 5', mRNA sequence). The predicted amino acid sequence disclosed herein for yb8_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted yb8_1 protein demonstrated at least some similarity to sequences identified as L10334 (neuroendocrine-specific proteins B and C [Homo sapiens]) and U17603 (rS-Rex-s [Rattus norvegicus]). Based upon sequence similarity, yb8_1 proteins and each similar protein or peptide may share at least some activity. The predicted yb8_1 protein shows significant (60% identity) amino acid similarity to the neuro-endocrine specific protein (NSP) family of proteins. Roebroek *et al.* (1993, *J. Biol Chem.* 268: 13439, which is incoporated by reference herein) report observing three transcripts from this gene family: NSP-A (3.4 kb), -B (2.3 kb), and -C (1.8 kb); they encode proteins of 776, 356, and 208 amino acids, respectively. Roebroek *et al.* also observe that these three transcripts are identical at the 3' end and only differ over a short portion near their 5' ends, and are thus possible splice variants. NSP-A and NSP-C were found in neural and endocrine tissues while NSP-B was found only in a lung carcinoma cell line (Roebrek *et al.* state that NSP-B is "aberrant" suggesting that it might be an artifact). The C-teminal portions of the protein sequences from all three transcripts are identical. The predicted yb8_1 protein shows strong amino acid similarity within this region and is about as long as NSP-C. Thus the predicted yb8_1 protein appears to be related to NSP-C. The TopPredII computer program predicts two potential transmembrane domains within the yb8_1 protein sequence, centered around amino acids 82 and 174 of SEQ ID NO:20, respectively.

Deposit of Clones

Clones bd306_7, fj283_11, fk317_3, k213_2x, na316_1, nf93_20, np164_1, pe204_1, ya1_1, and yb8_1 were deposited on November 26, 1997 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and were given the accession number ATCC 98599, from which each clone comprising a particular polynucleotide is obtainable. Clone fj283_6 was deposited on 17 November, 1998 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and was given the accession number ATCC xxxxx. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b), and the term of the deposit will comply with 37 C.F.R. § 1.806.

Each clone has been transfected into separate bacterial cells (*E. coli*) in the accession number ATCC 98599 composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Figures 1A and 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* **19**: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of an

oligonucleotide probe that was used to isolate or to sequence each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
bd306_7	SEQ ID NO:21
fj283_11	SEQ ID NO:22
fj283_6	SEQ ID NO:31
fk317_3	SEQ ID NO:23
k213_2x	SEQ ID NO:24
na316_1	SEQ ID NO:25
nf93_20	SEQ ID NO:26
np164_1	SEQ ID NO:27
pe204_1	SEQ ID NO:28
ya1_1	SEQ ID NO:29
yb8_1	SEQ ID NO:30

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as, for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with γ-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to

the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can

then be performed at an Internet site provided by the National Center for Biotechnology Information having the address http://www.ncbi.nlm.nih.gov/UniGene/, in order to identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* **15(7)**: 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* **62(1)**: 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* **58**: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* **14(9)**: 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* **90(16)**: 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* **91(2)**: 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* **336**: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms, part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information. For example, the TopPredII computer program can be used to predict the location of transmembrane domains in an amino acid sequence, domains which are described by the location of the center of the transmsmbrane domain, with at least ten transmembrane amino acids on each side of the reported central residue(s).

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* **266**: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* **215**: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, *Nature Genetics* **3**: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, *Proc. Natl. Acad. Sci. USA* **90**: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from ftp://blast.wustl.edu/blast/executables. The complete suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is

provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated from mammalian

species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes, Gorilla gorilla, Pongo pygmaeus, Hylobates concolor, Macaca mulatta, Papio papio, Papio hamadryas, Cercopithecus aethiops, Cebus capucinus, Aotus trivirgatus, Sanguinus oedipus, Microcebus murinus, Mus musculus, Rattus norvegicus, Cricetulus griseus, Felis catus, Mustela vison, Canis familiaris, Oryctolagus cuniculus, Bos taurus, Ovis aries, Sus scrofa,* and *Equus caballus,* for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682-690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, MA), Pharmacia (Piscataway, NJ) and Invitrogen Corporation (Carlsbad, CA), respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from the Eastman Kodak Company (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art

given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, those described in Gyuris *et al.*, 1993, *Cell* 75: 791-803 and in Rossi *et al.*, 1997, *Proc. Natl. Acad. Sci. USA* 94: 8405-8410, all of which are incorporated by reference herein) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may

induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols*

in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to

anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy.

Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a

cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation,

those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid

precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells.* R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long

term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as

well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation

of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al.

APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved

extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via antibody-dependent cell-mediated cytotoxicity (ADCC)). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s);

effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to

a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the

carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins

or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering

various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bd306_7 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bd306_7 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:2;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

2. The polynucleotide of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with the polynucleotide of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein encoded by the polynucleotide of claim 2, which process comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying said protein from the culture.

6. A protein produced according to the process of claim 5.

7. An isolated polynucleotide encoding the protein of claim 6.

8. The polynucleotide of claim 7, wherein the polynucleotide comprises the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599.

9. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 148 to amino acid 189;

(c) fragments of the amino acid sequence of SEQ ID NO:2 comprising eight consecutive amino acids of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

10. The protein of claim 9, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

11. The protein of claim 9, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 148 to amino acid 189.

12. A composition comprising the protein of claim 9 and a pharmaceutically acceptable carrier.

13. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:1, but excluding the poly(A) tail at the 3' end of SEQ ID NO:1; and

(ab) the nucleotide sequence of the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:1, but excluding the poly(A) tail at the 3' end of SEQ ID NO:1; and

(bb) the nucleotide sequence of the cDNA insert of clone bd306_7 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:1 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:1 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:1;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 1265; and

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:1 from nucleotide 132 to nucleotide 1265.

14. An isolated polynucleotide produced according to the process of claim 13.

15. An isolated polynucleotide comprising the polynucleotide of claim 14.

16. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 982 to nucleotide 2118;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 1042 to nucleotide 2118;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 621 to nucleotide 1248;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fj283_6 deposited under accession number ATCC xxxxx;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone fj283_6 deposited under accession number ATCC xxxxx;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:4; and

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above.

17. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) fragments of the amino acid sequence of SEQ ID NO:4 comprising eight consecutive amino acids of SEQ ID NO:4; and

(c) the amino acid sequence encoded by the cDNA insert of clone fj283_6 deposited under accession number ATCC xxxxx;

the protein being substantially free from other mammalian proteins.

18. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fk317_3 deposited under accession number ATCC 98599;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(f) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:6;

(g) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(h) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(f).

19. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 72;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising eight consecutive amino acids of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

20. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:5, but excluding the poly(A) tail at the 3' end of SEQ ID NO:5; and

(ab) the nucleotide sequence of the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:5, but excluding the poly(A) tail at the 3' end of SEQ ID NO:5; and

(bb) the nucleotide sequence of the cDNA insert of clone fk317_3 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:5 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:5 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:5; and

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:5 from nucleotide 259 to nucleotide 624.

21. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone k213_2x deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone k213_2x deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:8;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

22. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8 comprising eight consecutive amino acids of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone k213_2x deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

23. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:7, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:7; and

(ab) the nucleotide sequence of the cDNA insert of clone k213_2x deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:7, but excluding the poly(A) tail at the 3' end of SEQ ID NO:7; and

(bb) the nucleotide sequence of the cDNA insert of clone k213_2x deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:7 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:7 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:7;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 357 to nucleotide 578; and

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 471 to nucleotide 578.

24. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone na316_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone na316_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:10;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

25. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10 comprising eight consecutive amino acids of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone na316_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

26. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:9, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:9; and

(ab) the nucleotide sequence of the cDNA insert of clone na316_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:9, but excluding the poly(A) tail at the 3' end of SEQ ID NO:9; and

(bb) the nucleotide sequence of the cDNA insert of clone na316_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:9 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:9 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:9;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:9 from nucleotide 332 to nucleotide 598; and

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:9 from nucleotide 458 to nucleotide 598.

27. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone nf93_20 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone nf93_20 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:12;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

28. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) fragments of the amino acid sequence of SEQ ID NO:12 comprising eight consecutive amino acids of SEQ ID NO:12; and

(c) the amino acid sequence encoded by the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

29. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:11, but excluding the poly(A) tail at the 3' end of SEQ ID NO:11; and

(ab) the nucleotide sequence of the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:11, but excluding the poly(A) tail at the 3' end of SEQ ID NO:11; and

(bb) the nucleotide sequence of the cDNA insert of clone nf93_20 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:11 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:11 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:11;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:11 from nucleotide 354 to nucleotide 986; and

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:11 from nucleotide 408 to nucleotide 986.

30. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone np164_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone np164_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:14;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

31. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) fragments of the amino acid sequence of SEQ ID NO:14 comprising eight consecutive amino acids of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone np164_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

32. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:13, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:13; and

(ab) the nucleotide sequence of the cDNA insert of clone np164_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:13, but excluding the poly(A) tail at the 3' end of SEQ ID NO:13; and

(bb) the nucleotide sequence of the cDNA insert of clone np164_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:13 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:13 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:13;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:13 from nucleotide 301 to nucleotide 1821; and

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:13 from nucleotide 1381 to nucleotide 1821.

33. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 532 to nucleotide 537;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pe204_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone pe204_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:16;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

34. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) fragments of the amino acid sequence of SEQ ID NO:16 comprising eight consecutive amino acids of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

35. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:15, but excluding the poly(A) tail at the 3' end of SEQ ID NO:15; and

(ab) the nucleotide sequence of the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:15, but excluding the poly(A) tail at the 3' end of SEQ ID NO:15; and

(bb) the nucleotide sequence of the cDNA insert of clone pe204_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:15, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:15 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:15 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:15; and

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:15 from nucleotide 148 to nucleotide 537.

36. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ya1_1 deposited under accession number ATCC 98599;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone ya1_1 deposited under accession number ATCC 98599;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:18;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

37. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) fragments of the amino acid sequence of SEQ ID NO:18 comprising eight consecutive amino acids of SEQ ID NO:18; and

(c) the amino acid sequence encoded by the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

38. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:17, but excluding the poly(A) tail at the 3' end of SEQ ID NO:17; and

(ab) the nucleotide sequence of the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:17, but excluding the poly(A) tail at the 3' end of SEQ ID NO:17; and

(bb) the nucleotide sequence of the cDNA insert of clone ya1_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:17 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:17 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:17;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:17 from nucleotide 24 to nucleotide 1109; and

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:17 from nucleotide 1050 to nucleotide 1109.

39. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone yb8_1 deposited under accession number ATCC 98599;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone yb8_1 deposited under accession number ATCC 98599;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:20;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

40. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 70 to amino acid 236;

(c) fragments of the amino acid sequence of SEQ ID NO:20 comprising eight consecutive amino acids of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599;

the protein being substantially free from other mammalian proteins.

41. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:19, but excluding the poly(A) tail at the 3' end of SEQ ID NO:19; and

(ab) the nucleotide sequence of the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said probe(s) to human DNA; and

(iii) isolating the DNA polynucleotide detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:19, but excluding the poly(A) tail at the 3' end of SEQ ID NO:19; and

(bb) the nucleotide sequence of the cDNA insert of clone yb8_1 deposited under accession number ATCC 98599; and

(ii) hybridizing said primer(s) to human DNA;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii);

wherein the isolated polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(v) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:19 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:19 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:19;

(w) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 27 to nucleotide 734;

(x) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734, to a nucleotide sequence corresponding to

the 3' end of said sequence of SEQ ID NO:19 from nucleotide 270 to nucleotide 734; and

(y) a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 85 to nucleotide 1604.

FIGURE 1A

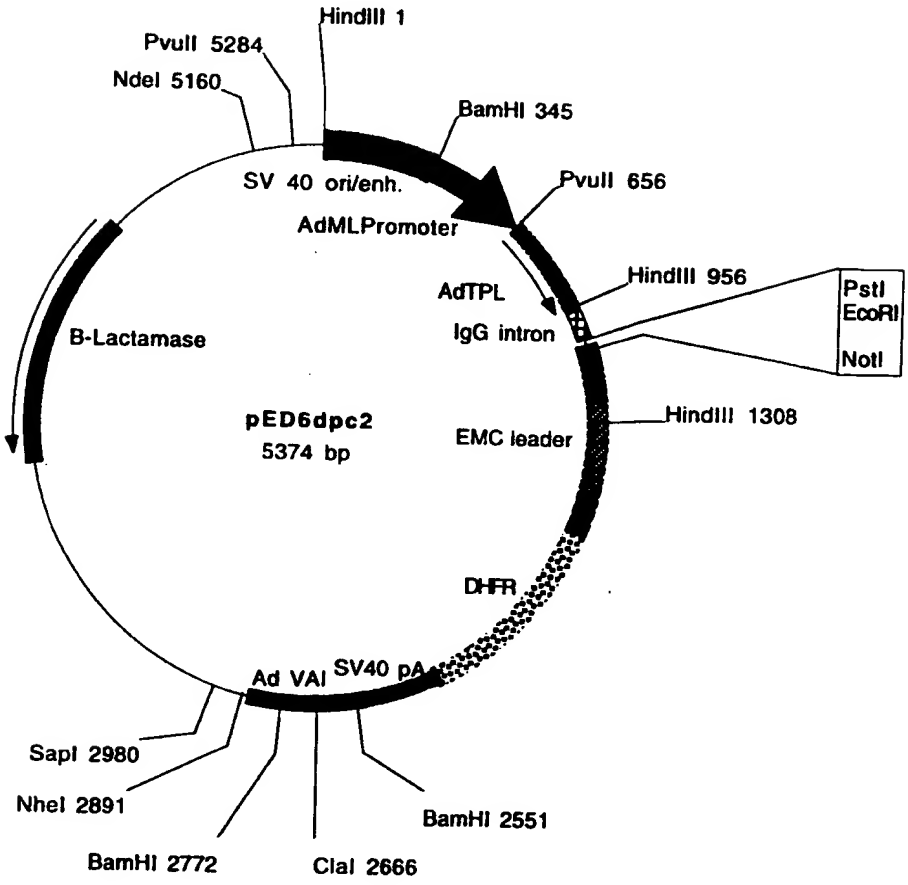
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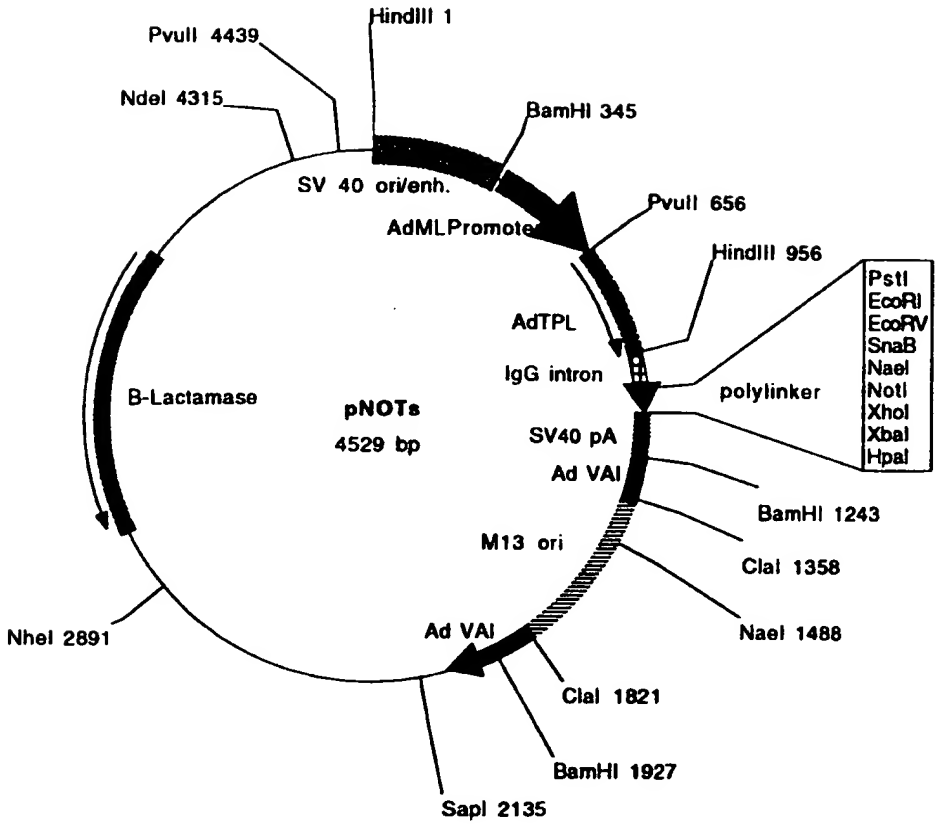
FIGURE 1B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<210> 4
<211> 379
<212> PRT
<213> Homo sapiens

<400> 4
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Gly Ala Gly Ala Cys Tyr Cys Ile Tyr Arg Leu Thr Arg Gly Arg Lys
             20                  25                  30

Gln Asn Lys Glu Lys Met Ala Glu Gly Gly Ser Gly Asp Val Asp Asp
         35                  40                  45

Ala Gly Asp Cys Ser Gly Ala Arg Tyr Asn Asp Trp Ser Asp Asp Asp
     50                  55                  60

Asp Asp Ser Asn Glu Ser Lys Ser Ile Val Trp Tyr Pro Pro Trp Ala
 65                  70                  75                  80

Arg Ile Gly Thr Glu Ala Gly Thr Arg Thr Arg Ala Arg Ala Arg Ala
                 85                  90                  95

Arg Ala Thr Arg Ala Arg Leu Ala Val Gln Lys Arg Ala Ser Pro Asn
            100                 105                 110

Ser Asp Asp Thr Val Leu Ser Pro Gln Glu Leu Gln Lys Val Leu Cys
        115                 120                 125

Leu Val Glu Met Ser Glu Lys Pro Tyr Ile Leu Glu Ala Ala Leu Ile
    130                 135                 140

Ala Leu Gly Asn Asn Ala Ala Tyr Ala Phe Asn Arg Asp Ile Ile Arg
145                 150                 155                 160

Asp Leu Gly Gly Leu Pro Ile Val Ala Lys Ile Leu Asn Thr Arg Asp
                165                 170                 175

Pro Ile Val Lys Glu Lys Ala Leu Ile Val Leu Asn Asn Leu Ser Val
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            180                 185                 190

Asn Ala Glu Asn Gln Arg Arg Leu Lys Val Tyr Met Asn Gln Val Cys
        195                 200                 205

Asp Asp Thr Ile Thr Ser Arg Leu Asn Ser Ser Val Gln Leu Ala Gly
    210                 215                 220

Leu Arg Leu Leu Thr Asn Met Thr Val Thr Asn Glu Tyr Gln His Met
225                 230                 235                 240

Leu Ala Asn Ser Ile Ser Asp Phe Phe Arg Leu Phe Ser Ala Gly Asn
                245                 250                 255

Glu Glu Thr Lys Leu Gln Val Leu Lys Leu Leu Leu Asn Leu Ala Glu
            260                 265                 270

Asn Pro Ala Met Thr Arg Glu Leu Leu Arg Ala Gln Val Pro Ser Ser
        275                 280                 285

Leu Gly Ser Leu Phe Asn Lys Lys Glu Asn Lys Glu Val Ile Leu Lys
    290                 295                 300

Leu Leu Val Ile Phe Glu Asn Ile Asn Asp Asn Phe Lys Trp Glu Glu
305                 310                 315                 320

Asn Glu Pro Thr Gln Asn Gln Phe Gly Glu Gly Ser Leu Phe Phe Phe
                325                 330                 335

Leu Lys Glu Phe Gln Val Cys Ala Asp Lys Val Leu Gly Ile Glu Ser
            340                 345                 350

His His Asp Phe Leu Val Lys Val Lys Val Gly Lys Phe Met Ala Lys
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Leu Ala Glu His Met Phe Pro Lys Ser Gln Glu
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<210> 5
<211> 1608
<212> DNA
<213> Homo sapiens

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aattcttaaa ttcaatgcaa ggagtttttg ctgagtatct gcagcattca aggaattaat 180
attagtcact gagaacaaaa agcgaaatta gaaaatttca agtcacttct aggcttgtag 240
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<210> 6
<211> 122
<212> PRT
<213> Homo sapiens

<400> 6
Met Asn Ser Ile Ile Tyr Glu Val Pro Thr Gly Ser His Thr Leu Cys
1 5 10 15

Lys Thr Phe Arg Ser Gly Ala Ser Leu Gly Phe Leu His Pro Val Gln
20 25 30

Gln Val Leu Leu Phe Pro Phe Leu Asn Tyr Tyr Leu Leu Leu Leu Phe
35 40 45

Phe Glu Thr Gly Ser Pro Phe Val Thr Gln Ala Gly Met Gln Arg His
50 55 60

Asp His Cys Ser Leu Gln Leu Arg Pro Pro Arg Leu Lys Gly Val Ser
65 70 75 80

His Leu Gly Cys Cys His Thr Trp Pro Thr Phe Leu Tyr Phe Phe Gly
85 90 95

Arg Asp Arg Gly Phe Thr Met Leu Pro Arg Leu Val Leu Asn Phe Trp
100 105 110

Thr Pro Ala Ile Cys Leu Pro Pro Pro Pro
115 120

<210> 7
<211> 1969
<212> DNA
<213> Homo sapiens

<400> 7
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aagaaaacat tgcaaaagct aaacgactaa aaaaggattg aaggactgaa caggctttgc 600

aaccagagga aaatcatttg gaaaattaca cagctttgga agaatccact aaagtttctt 660
ctttggattt cttgacagta tgatttagta aatgaaattt gaccaaatgg aagaatcatg 720
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<210> 8
<211> 74
<212> PRT
<213> Homo sapiens

<400> 8
Met Phe Asp Ile Lys Ala Trp Ala Glu Tyr Val Val Glu Trp Ala Ala
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Lys Asp Pro Tyr Gly Phe Leu Thr Thr Val Ile Leu Ala Leu Thr Pro
20 25 30

Leu Phe Leu Ala Ser Ala Val Leu Ser Trp Lys Leu Ala Lys Met Ile
35 40 45

Glu Ala Arg Glu Lys Glu Gln Lys Lys Lys Gln Lys Arg Gln Glu Asn
50 55 60

Ile Ala Lys Ala Lys Arg Leu Lys Lys Asp
65 70

<210> 9
<211> 819
<212> DNA
<213> Homo sapiens

<400> 9
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gagcagagga gagtcagcag tctctaaatt atcatcatct cctacctgca catgtacaca 180
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cagagggcca aaaagaaaat tccatgagga catgagagtg cattgaggtt gcaggtatac 300
agtcaccaaa gaacctgaaa taattgccgg aatgatatcc tctaaaagat gtgagcctct 360
cagagagaga gagagagggt tcctcttgca acaggcatcg tgtgtgtgtt ttatgtccct 420
tctcttctgc tgctgtgcac ttaattcggt tccagccgtg tcagggagac tcgagaaaaa 480

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<210> 10
<211> 89
<212> PRT
<213> Homo sapiens

<400> 10
Met Ile Ser Ser Lys Arg Cys Glu Pro Leu Arg Glu Arg Glu Arg Gly
  1               5                  10                  15

Phe Leu Leu Gln Gln Ala Ser Cys Val Cys Phe Met Ser Leu Leu Phe
             20                  25                  30

Cys Cys Cys Ala Leu Asn Ser Val Pro Ala Val Ser Gly Arg Leu Glu
         35                  40                  45

Lys Lys Ile Pro Pro Leu Lys Thr Cys Ser Leu Phe Phe Gln Ser Val
     50                  55                  60

Thr Pro Ala Ile Ser Leu Ala Ser His Gly Ser Val Asn Trp His Thr
 65                  70                  75                  80

Ala Ala Val Arg Gln Trp Lys Lys Ser
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<210> 11
<211> 1969
<212> DNA
<213> Homo sapiens

<400> 11
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<210> 12
<211> 211
<212> PRT
<213> Homo sapiens

<400> 12

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Met Val Phe Leu Lys Phe Phe Cys Met Ser Phe Phe Cys His Leu Cys
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Gln Gly Tyr Phe Asp Gly Pro Leu Tyr Pro Glu Met Ser Asn Gly Thr
             20                  25                  30

Leu His His Tyr Phe Val Pro Asp Gly Asp Tyr Glu Glu Asn Asp Asp
         35                  40                  45

Pro Glu Lys Cys Gln Leu Leu Phe Arg Val Ser Asp His Arg Arg Cys
     50                  55                  60

Ser Gln Gly Glu Gly Ser Gln Val Gly Ser Leu Leu Ser Leu Thr Leu
 65                  70                  75                  80

Arg Glu Glu Phe Thr Val Leu Gly Arg Gln Val Glu Asp Ala Gly Arg
                 85                  90                  95

Val Leu Glu Gly Ile Ser Lys Ser Ile Ser Tyr Asp Leu Asp Gly Glu
            100                 105                 110

Glu Ser Tyr Gly Lys Tyr Leu Arg Arg Glu Ser His Gln Ile Gly Asp
        115                 120                 125

Ala Tyr Ser Asn Ser Asp Lys Ser Leu Thr Glu Leu Glu Ser Lys Phe
    130                 135                 140

Lys Gln Gly Gln Glu Gln Asp Ser Arg Gln Glu Ser Arg Leu Asn Glu
145                 150                 155                 160

Asp Phe Leu Gly Met Leu Val His Thr Arg Ser Leu Leu Lys Glu Thr
                165                 170                 175

Leu Asp Ile Ser Val Gly Leu Arg Asp Lys Tyr Glu Leu Leu Ala Leu
            180                 185                 190

Thr Ile Arg Ser His Gly Thr Arg Leu Gly Arg Leu Lys Asn Asp Tyr
        195                 200                 205

Leu Lys Val
    210
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<210> 13
<211> 2020
<212> DNA
<213> Homo sapiens

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<210> 14
<211> 507
<212> PRT
<213> Homo sapiens

<220>
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<222> (439)

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<222> (476)

<400> 14

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Val Arg Trp Thr Val Ser Leu Asn Ser Tyr Ser Gly Ala Gly Lys Pro
             20                  25                  30

Pro Met Phe Gly Asp Tyr Glu Ala Gln Arg His Trp Gln Glu Ile Thr
         35                  40                  45

Phe Asn Leu Pro Val Lys Gln Trp Tyr Phe Asn Ser Ser Asp Asn Asn
     50                  55                  60

Leu Gln Tyr Trp Gly Leu Asp Tyr Pro Pro Leu Thr Ala Tyr His Ser
 65                  70                  75                  80

Leu Leu Cys Ala Tyr Val Ala Lys Phe Ile Asn Pro Asp Trp Ile Ala
                 85                  90                  95

Leu His Thr Ser Arg Gly Tyr Glu Ser Gln Ala His Lys Leu Phe Met
            100                 105                 110

Arg Thr Thr Val Leu Ile Ala Asp Leu Leu Ile Tyr Ile Pro Ala Val
        115                 120                 125

Val Leu Tyr Cys Cys Cys Leu Lys Glu Ile Ser Thr Lys Lys Lys Ile
    130                 135                 140

Ala Asn Ala Leu Cys Ile Leu Leu Tyr Pro Gly Leu Ile Leu Ile Asp
145                 150                 155                 160

Tyr Gly His Phe Gln Tyr Asn Ser Val Ser Leu Gly Phe Ala Leu Trp
                165                 170                 175

Gly Val Leu Gly Ile Ser Cys Asp Cys Asp Leu Leu Gly Ser Leu Ala
            180                 185                 190

Phe Cys Leu Ala Ile Asn Tyr Lys Gln Met Glu Leu Tyr His Ala Leu
        195                 200                 205

Pro Phe Phe Cys Phe Leu Leu Gly Lys Cys Phe Lys Lys Gly Leu Lys
    210                 215                 220

Gly Lys Gly Phe Val Xaa Leu Val Lys Leu Ala Xaa Ile Val Val Ala
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Ser Phe Val Leu Cys Trp Leu Pro Phe Phe Thr Glu Arg Glu Gln Thr
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Ser Ser Lys Gly Phe Lys Phe Thr Leu Val Ser Cys Ala Leu Ser Phe
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Glu Leu Leu Met Pro Ser Val Val Thr Thr Met Ala Phe Phe Ile Ala
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Cys Val Thr Ser Phe Ser Ile Phe Glu Lys Thr Ser Glu Glu Glu Leu
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Gln Leu Lys Ser Phe Ser Ile Ser Val Arg Lys Tyr Leu Pro Cys Xaa
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Val Phe Gln Ala Gly Leu Val Asn Leu Leu Phe His Lys Phe Lys Gly
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Thr Ile Ile Leu Thr Ala Val Tyr Phe Ala Leu Ser Ile Ser Leu His
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Val Trp Val Met Asn Leu Arg Trp Lys Asn Ser Asn Ser Phe Ile Trp
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Gly Asn Asp Lys His Lys Leu Thr Ser Ala Gly Phe Phe Val Glu Leu
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Ile Cys Ala Gln Phe Leu Lys Trp Lys Leu Pro Gln Glu Val Tyr Ser
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Lys Asp Pro Trp His Ile Lys Pro Thr Glu Ala Gly Thr Ile Cys Arg
                245                 250                 255

Phe Phe Glu Lys Lys Cys Lys Gly Lys Ile Asn Ile Leu Glu Gln Thr
            260                 265                 270

Leu Met Tyr Ser Lys Asn Pro Lys Leu Pro Ile Arg Arg Ser Ala Val
        275                 280                 285

Leu Phe Val Gly Leu Leu Ser Lys Tyr Met Asp His Asn Glu Leu Arg
    290                 295                 300

Arg Met Gly Thr Asp Trp Ile Glu Asp Asp Leu Arg Asp Leu Leu Cys
305                 310                 315                 320

Asp Pro Glu Pro Ser Leu Cys Ile Ile Ala Ser Gln Thr Leu Leu Leu
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Gly Thr Thr Leu Ile Met Leu Leu Ser Leu Ala Ala Phe Ser Val Ile
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Ser Val Val Ser Tyr Leu Ile Leu Ala Leu Leu Ser Val Thr Ile Ser
85 90 95

Phe Arg Ile Tyr Lys Ser Val Ile Gln Ala Val Gln Lys Ser Glu Glu
100 105 110

Gly His Pro Phe Lys Ala Tyr Leu Asp Val Asp Ile Thr Leu Ser Ser
115 120 125

Glu Ala Phe His Asn Tyr Met Asn Ala Ala Met Val His Ile Asn Arg
130 135 140

Ala Leu Lys Leu Ile Ile Arg Leu Phe Leu Val Glu Asp Leu Val Asp
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Ser Leu Lys Leu Ala Val Phe Met Trp Leu Met Thr Tyr Val Gly Ala
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Val Phe Asn Gly Ile Thr Leu Leu Ile Leu Ala Glu Leu Leu Ile Phe
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25149

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1, 252.3, 320.1, 91.1, 91.2; 536/23.1, 23.5, 24.31; 530/350; 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog and APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database EMBL/GenBank, Isolation and Characterization of a cDNA Encoding a Synaptonemal Complex Protein. Accessions A56822; S20742.Biochem. Cell Biol., 1992, Vol. 70, pages 1030-1038, Chen et al. 10-September-1997, see entire document.	1-15
Y	CHEN et al. Isolation and Characterization of a cDNA Encoding a Synaptonemal Complex Protein. Biochem. Cell Biol. (1992) Vol. 70, pages 1030-1038, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 FEBRUARY 1999	Date of mailing of the international search report 08 MAR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ENRIQUE D. LONGTON Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25149

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-15

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25149

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07H 21/04, 21/02; C12N 15/11, 15/00, 1/21, 15/63; C07K 14/00; A61K 38/00; C12P 19/34

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/69.1, 252.3, 320.1, 91.1, 91.2; 536/23.1, 23.5, 24.31; 530/350; 514/12

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-15, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:1 and 2 as well as processes for producing the polynucleotides and polypeptides.
Group II, claim(s) 16-17, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:32 and 4 as well as processes for producing the polynucleotides and polypeptides.
Group III, claim(s) 18-20, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:5 and 6 as well as processes for producing the polynucleotides and polypeptides.
Group IV, claim(s) 21-23, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:7 and 8 as well as processes for producing the polynucleotides and polypeptides.
Group V, claim(s) 24-26, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:9 and 10 as well as processes for producing the polynucleotides and polypeptides.
Group VI, claim(s) 27-29, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:11 and 12 as well as processes for producing the polynucleotides and polypeptides.
Group VII, claim(s) 30-32, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:13 and 14 as well as processes for producing the polynucleotides and polypeptides.
Group VIII, claim(s) 33-35, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:15 and 16 as well as processes for producing the polynucleotides and polypeptides.
Group IX, claim(s) 36-38, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:17 and 18 as well as processes for producing the polynucleotides and polypeptides.
Group X, claim(s) 39-41, drawn to isolated polynucleotides and polypeptides related to or encoding SEQ ID NOS:19 and 20 as well as processes for producing the polynucleotides and polypeptides.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The claims of each group are directed to separate and distinct polynucleotide and polypeptide sequences structurally unrelated, each to the other. Therefore, the inventions lack the same or corresponding special technical feature.